SUMMARY. The antianginal effects of beta-adrenoceptor antagonists are achieved by a reduction in myocardial oxygen demand. This is a rational approach to treatment in patients whose angina is caused by a fixed stenosis. However, dynamic coronary vasospasm is an important factor in patients with chronic stable angina. Nifedipine increases myocardial oxygen supply by reducing coronary vascular tone and is a logical approach to treatment in these patients. For monotherapy of angina, nifedipine is less effective than the beta-adrenoceptor antagonists, but the combination has additive effects in reducing the frequency of anginal episodes and improving exercise tolerance.

Plasma concentrations of nifedipine are closely related to clinical efficacy, and the variable first-pass metabolism of the drug leads to wide interindividual differences in peak concentrations and duration of action. Increasing the size of individual doses of nifedipine carries a risk of enhanced side effects due to high peak plasma concentrations. Optimal treatment may be more appropriately achieved in some patients by a slow release formulation, but with an increased frequency of administration.

KEY WORDS. beta-adrenoceptor antagonist, nifedipine, angina pectoris

Considerable advances have been made in the pharmacologic management of angina pectoris during the last 20 years. Improved understanding of the pathophysiological mechanisms that produce myocardial ischemia has led to a more rational and effective approach to treatment. Beta-adrenoceptor antagonists are well established for the prophylactic management of chronic stable angina pectoris [1–3], but even with optimal doses some patients will require additional treatment to achieve adequate control of symptoms. Slow-channel calcium blockers are increasingly used in this situation as an alternative to long-acting nitrates. The calcium antagonists are a heterogenous group of compounds, and of these the dihydropyridine derivatives, such as nifedipine, have properties that make them particularly suitable for combination with beta-adrenoceptor antagonists. Increasing numbers of dihydropyridine derivatives are now undergoing investigation, and it is therefore opportune to review their efficacy in this situation.

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ence of damaged endothelium, vasoconstriction occurs. On the other hand, nitrates are vasodilators, even in the presence of endothelial damage. Endothelium-dependent vasodilators are believed to act through the unstable humoral agent, endothelium-derived relaxing factor (EDRF) [11].

Until recently it was believed that myocardial ischemia in stable angina pectoris occurred when an increase in myocardial work exceeded oxygen delivery from a fixed maximum blood supply. This classic concept of an increased oxygen demand exceeding a fixed blood supply will apply only in the presence of fixed atheromatous stenosis, when an increase in sympathetic drive, such as occurs with exercise or emotion, increases heart rate and blood pressure. The increase in heart rate will influence myocardial blood flow, since diastolic relaxation time is reduced, impairing subendocardial vessels due to the increased myocardial contractility. Secondly, tachycardia increases myocardial oxygen consumption, leading to metabolic vasodilatation in the juxtaischemic region, which may cause a transmural “steal” phenomenon, further reducing subendocardial flow. The increase in aortic blood pressure leads to passive dilatation of large epicardial arteries and an increase in the velocity of coronary blood flow. This results in a drop in pressure across a distal coronary stenosis, maximum at its point of greatest narrowing, further reducing subendocardial perfusion. A fall in perfusion pressure may also cause passive collapse of the coronary lumen at the site of stenosis.

Recently the work of Brown et al [12] and Maseri and co-workers [13, 14], among others, has suggested that the obstruction to coronary blood flow can be variable. Brown et al [12] have demonstrated the complex interaction between blood flow, trans-stenotic perfusion pressure drop, the morphology of the atherosclerotic lesions, and the mechanisms of arterial tone in the genesis of the various anginal syndromes. Only a minority of patients have a fixed luminal diameter due to circumferential atheromatous narrowing. In over 70% of cases, the stenoses are eccentric and are partially circumscribed by an arc of normal arterial wall [15] which may respond to fluctuations in intraluminal pressure and/or vasomotor tone, to alter the diameter of the lumen.

Of particular interest regarding the mechanism of action of both calcium antagonists and beta-adrenoceptor antagonists is the influence of alpha-adrenoceptor-mediated vasoconstrictor tone. Nabel and others [16] have shown that alpha-adrenoceptor stimulation of normal coronary arteries leads to vasodilatation—probably due to reflex release of EDRF. However, in the presence of endothelial damage (as occurs with atheromatous stenosis), vasoconstriction occurs. During experimental limitation of coronary flow, Feigl [4] demonstrated an unexpected beneficial effect of alpha-adrenoceptor-mediated coronary vasoconstriction that may reduce the transmural steal effect by a preferential effect on epicardial vessels, thus preserving subendocardial flow. In contrast, Brown et al. [12] suggested that in the presence of eccentric atheroma, even a small increase in vasomotor tone can exacerbate ischemia across a critical stenosis. In support of this theory, alpha-adrenoceptor-mediated vasoconstriction has been shown experimentally to exacerbate myocardial ischemia when the balance between oxygen supply and demand is very unfavorable [17]. The net effects of altered alpha-adrenoceptor-mediated coronary vasomotor tone appear to be governed by the degree of ischemia, the size of the vessel preferentially affected, and probably also the modulating effects of circulating and local vasoactive substances.

To explain the various manifestations of stable angina, Brown et al. [12] postulated that in patients with circumferential atheroma, a moderate fixed stenosis, and little or no “free wall,” myocardial oxygen supply is limited only by coronary atheroma and exercise tolerance will be predictable. Eccentric atheroma has a large amount of free wall, and fluctuations in vasomotor tone will play a larger role in determining lumen diameter. Exercise tolerance in these patients is more variable. Maseri et al. [13, 14] extended these views, suggesting that in stable angina pectoris (as well as unstable and variant angina), there are both active and quiescent phases of obstruction. These concepts apply to both painful and painless or silent ischemia, since asymptomatic episodes are not preceded by a significant increase in heart rate on all occasions.

The Mechanism of Action of Beta-Adrenoceptor Antagonists, Calcium Antagonists, and their Combination in Stable Angina

The hypothesis that both fixed and dynamic stenoses are important in stable angina has considerable implications for management. Beta-adrenoceptor antagonists exert their antianginal effects primarily by competitive inhibition of catecholamines at cardiac beta adrenoceptors. The consequent reduction in heart rate (particularly the rise with exercise), and the lesser effects on myocardial contractility and systemic blood pressure reduces myocardial oxygen demand. These actions are partially offset by the increased ejection